

Prediction of Cardiovascular Events in Clinically Selected High-Risk NIDDM Patients

Prognostic value of exercise stress test and thallium-201 single-photon emission computed tomography

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OBJECTIVE — We evaluated the prognostic value of an exercise stress test and thallium-201 scintigraphy for the prediction of cardiac events in selected high-risk NIDDM patients.

RESEARCH DESIGN AND METHODS — NIDDM patients ($n = 158$, 105 men, aged 63 ± 9 years) with two or more of the following criteria were prospectively included: age ≥ 65 years, active smoking, hypertension $>160/95$ mmHg, hypercholesterolemia (cholesterol >5.70 mmol/l or LDL >3.10 mmol/l), peripheral artery disease, abnormal rest electrocardiogram, or microalbuminuria (20–200 $\mu\text{g}/\text{min}$). An exercise-stress scintigraphy was performed in 77 patients able to exercise, while a dipyridamole scintigraphy was performed in 80 patients unable to exercise. Follow-up was 23 ± 17 months. Major end points were cardiac deaths or nonfatal myocardial infarction.

RESULTS — The annual event rate was 7.31% (deaths: 8, myocardial infarction: 14). Independent predictors of events were as follows: an age >60 ($P = 0.02$), an abnormal rest electrocardiogram ($P = 0.02$), microalbuminuria ($P = 0.001$), the inability to exercise ($P = 0.009$), and the presence of more than two defects on scintigraphy ($P = 0.001$). A cardiac death occurred in 1.3% of patients able to exercise versus 8.8% of patients unable to exercise (odds ratio = 6.8, $P = 0.001$). Among patients unable to exercise, large perfusion defects corresponded to an annual mortality rate of 22.3%. Conversely, the negative predictive value of a normal scintigraphy for the occurrence of death was 97%.

CONCLUSIONS — Inability to exercise and large perfusion defects on thallium-201 scan are major predictors of future death and myocardial infarction in high-risk NIDDM patients.

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More than 50% of diabetic patients die from cardiovascular causes (1), and risk of cardiac death is three times higher in diabetic than in nondiabetic patients (2,3). Furthermore, consequences

of coronary artery disease (CAD) are more severe (4,5). Because myocardial ischemia is often silent (6–9), the prediction of major cardiovascular events in asymptomatic or mildly symptomatic NIDDM patients is a

fundamental issue. Several factors are acknowledged as prognostic indicators. Some are nonspecific (age, body weight, hypertension, dyslipidemia), while others are specific to NIDDM (dysautonomia [10], microalbuminuria [11]). Besides these clinical and biological factors, further investigations are required to identify very high-risk patients who may benefit from specific approaches such as invasive coronary investigations.

The exercise stress test (EST) has been proposed as one of these investigations (12,13), but is considered to be less specific in NIDDM patients than in the general population. Thallium-201 (^{201}Tl) single-photon emission computed tomography (SPECT) seems to be an ideal candidate, since its prognostic value is established in nondiabetic patients with a low to intermediate (14,15) or high (16) prevalence of CAD and in asymptomatic high-risk patients (17,18). Its prognostic value in diabetic patients, however, remains to be debated (19–26).

So far, the prognostic value of clinical, biological, EST, and ^{201}Tl SPECT data has not been specifically addressed in a homogeneous cohort of high-risk NIDDM patients. Therefore, we aimed to prospectively evaluate the prognostic value of EST and ^{201}Tl SPECT for the prediction of cardiac events in this setting.

RESEARCH DESIGN AND METHODS

Inclusion criteria

Between 1989 and 1994, NIDDM patients referred to the diabetes clinic were considered for inclusion. NIDDM was defined by diagnosis after the age of 40 years, with a familial history of diabetes, without history of ketosis, and without insulin treatment in the 2 years following diagnosis (27). Patients were prospectively included if they were considered to be at risk for future cardiac events because they presented with two or more of the criteria listed in Table 1.

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Abbreviations: CAD, coronary artery disease; CK, creatinine kinase; ECG, electrocardiogram; EST, exercise stress test; MI, myocardial infarction; NPV, negative predictive value; PPV, positive predictive value; ^{201}Tl , thallium-201; SPECT, single-photon emission computed tomography.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—Inclusion and exclusion criteria

Inclusion criteria
NIDDM patients presenting with two or more of the following risk factors
Age \geq 65 years
Active smoking
High blood pressure (\geq 160/95 mmHg)
Hypercholesterolemia (total cholesterol $>$ 5.70 mmol/l or LDL cholesterol $>$ 3.10 mmol/l)
History of coronary artery disease
Peripheral vascular disease
Abnormal rest electrocardiogram
Microalbuminuria (20–200 μ g/min)
Exclusion criteria
Myocardial revascularization $<$ 3 months
Episode of unstable angina $<$ 3 months
Acute myocardial infarction $<$ 3 months
Severe angina under medical therapy

The study population consisted of 158 patients. There were 75 (47.5%), 64 (40.5%), and 19 (12%) patients who presented with two to three, four to five, and six or more risk factors, respectively, and 124 of them (78%) were asymptomatic at the time of inclusion. Baseline characteristics of the study population are summarized in Table 2.

Functional capacity was then assessed by estimation of daily life activity according to a scale adapted from Taylor et al. (28). Patients with an estimated physical activity \geq 5 metabolic equivalents ($n = 78$) were classified as “able to exercise” and were scheduled for an EST coupled with a ^{201}Tl SPECT. Patients with an estimated physical activity $<$ 5 metabolic equivalents (obesity $n = 12$, chronic fatigue $n = 10$, peripheral neuropathy $n = 10$, pulmonary disease $n = 7$), as well as patients with peripheral vascular disease ($n = 25$), heart failure with exertional dyspnea class II or III by the New York Heart Association ($n = 8$), or previous cerebrovascular accident ($n = 8$), were classified as “unable to exercise” ($n = 80$) and were proposed for a pharmacological stress ^{201}Tl SPECT.

Stress tests

EST was performed on an ergometer bicycle starting at a 25-W step with an increase of 25-W increments every 3 min to achieve \geq 85% of maximum age-predicted heart rate. A 12-lead electrocardiogram (ECG) was continuously recorded and digitized (Marquette Case; Marquette Electronics, Milwaukee, WI) for delayed analysis. EST

Table 2—Baseline data

<i>n</i>	158
Clinical variables	
Sex (M/F)	105/53
Age (years)	63 \pm 9
BMI (kg/m ²)	28.7 \pm 5.6
Risk factors	
Number of risk factors per patient	3.9 \pm 1.5
Hypertension $>$ 160/95 mmHg	84 (53)
Serum cholesterol (mmol/l)	6.20 \pm 1.81
Serum HDL cholesterol (mmol/l)	1.03 \pm 0.26
Serum triglycerides (mmol/l)	3.63 \pm 4.20
Medical history	
Family history of CAD	65 (41)
Previous suspected or known CAD	47 (30)
Previous typical or equivocal angina	27 (17)
Previous MI	20 (13)
Congestive heart failure	9 (4)
Cerebrovascular accident	16 (10)
Peripheral vascular disease	43 (27)
Concomitant medications at inclusion	
Aspirin	36 (23)
Calcium antagonists	28 (18)
β -blockers	12 (8)
Clinical presentation at inclusion	
No symptoms	124 (78)
Equivocal chest pain	22 (14)
Typical angina	12 (8)
Rest electrocardiogram	
Normal	62 (39)
Q waves	37 (23)
ST depression	27 (17)
Ability to exercise	78 (49)
Diabetes	
Duration (years)	14 \pm 9
Insulin therapy	53 (35)
Dose of insulin (IU/day)	28 \pm 6
Fasting blood glucose (mmol/l)	9.45 \pm 3.33
HbA _{1c} (%)	8.1 \pm 1.7
Diabetic retinopathy	
Absent	78 (49)
Mild to moderate	52 (33)
Severe	28 (18)
Renal status	
Serum creatinine (μ mol/l)	99 \pm 64
Glomerular filtration (ml/s)	1.44 \pm 0.65
Microalbuminuria (20–200 μ g/min)	51 (32)
Proteinuria ($>$ 200 μ g/min)	33 (21)
Chronic hemodialysis	8 (5)

Data are *n*, means \pm SD, or *n* (%).

was considered to be positive in cases of horizontal or downsloping ST depression $>$ 1 mm measured 0.08 s after the J point. In patients with initial ST abnormalities on rest ECG, EST was considered to be positive when ST depression was $>$ 2 mm dur-

ing exercise (29). EST was stopped in cases of ST segment depression \geq 2 mm with or without chest pain. Pharmacological stress was performed using an intravenous infusion of dipyridamole (0.56 mg/kg body wt) over 4 min.

Table 3—Events at follow-up

Event	n (%)	Annual event rate (%/year)
Death	8 (5.0)	2.6
Sudden death	3 (1.9)	
Death following an acute MI	5 (3.1)	
Nonfatal MI	14 (8.9)	4.7
Symptomatic	8 (5.1)	
Silent (diagnosed on survey ECG)	6 (3.8)	
Major event (death or MI)	22 (13.9)	7.3
Minor event	29 (18.4)	9.7
Unstable angina	13 (8.2)	
Congestive heart failure	8 (5.1)	
Need for myocardial revascularization	8 (5.1)	
Any cardiovascular event	51 (32.3)	17.0

²⁰¹Tl SPECT

At the end of the stress tests, 2.5 mCi (92.5 MBq) of ²⁰¹Tl were injected intravenously, and initial images were recorded 10 min later. At 3 h after the stress, 1 mCi (37.5 MBq) of ²⁰¹Tl was injected at rest, and a new acquisition was performed 15 min later for reinjection imaging. The imaging protocol has been previously described (14). Briefly, the camera was rotated through a 180° circular orbit, and 32 projections were acquired over 20 min. Transaxial sections were obtained and reoriented according to the three standard cardiac planes (short, horizontal long, and vertical axes). The left ventricle was divided into nine segments, and scans were visually analyzed by two experienced observers blinded from clinical data. Each segment was classified as normal or abnormal, and if abnormal as reversible (partial or total normalization after reinjection) or fixed (persistent defect after reinjection). ²⁰¹Tl lung uptake was measured over the mid-left lung field in the anterior view before background subtraction. The lung-to-heart ²⁰¹Tl ratio was expressed as the ratio of the counts from 5 × 5 pixel regions of interest in the lung and the myocardium demonstrating the highest count activity.

Data collection and follow-up

Variables collected at inclusion were: age, sex, body weight, BMI, history of angina, myocardial infarction (MI) or heart failure, hypertension, smoking habits, cholesterolemia, presence of Q waves or ST segment elevation, and depression ≥1 mm on rest ECG. Other variables relative to NIDDM were also taken into consideration: need for insulin therapy and its cumulative

daily dose, fasting blood glycemia, HbA_{1c} (high-performance liquid chromatography, $n = 4.4$ – 5.8%). The presence of a nephropathy was searched by measurement of microalbuminuria (immunoturbidimetry; Behring, Marburg, Germany), dosage of proteinuria, serum creatinine levels, and glomerular filtration rates (creatinine clearance). Diabetic retinopathy was assessed by an experienced ophthalmologist through dilated pupils by direct ophthalmoscopy and biomicroscopy with the Goldman three-mirror lens. Mild to moderate retinopathy was diagnosed if at least one microaneurysm or hemorrhage or exudate in either eye was observed. Severe retinopathy was diagnosed when extensive ischemia and/or proliferation of neovessels had occurred.

Follow-up data were prospectively collected. At the end of the study, each patient underwent a systematic cardiology clinic and a rest ECG. For deceased patients, information was obtained by telephone from the family and the general practitioner. When complementary information was required, the cardiologist was also contacted.

Predetermined primary end points (major events) were as follows: cardiac deaths (sudden death or a death caused by MI or congestive heart failure) and symptomatic or silent nonfatal MIs. Symptomatic MI was defined by serum creatinine kinase (CK) level >240 U/l with creatinine kinase MB-isoform (MB-CK) isoenzymes >15 U, associated with new Q waves ≥0.04 s on the 12-lead ECG, or ST segment depression >1 mm 60 ms after the J point for non-Q wave MI. Silent MI was defined by the appearance of new Q waves on the ECG performed during survey.

Secondary end points (minor events) were as follows: unstable angina (reversible ischemic ST changes, i.e., ST segment depression or elevation ≥1 mm, with clinical symptoms and CK <240 U), acute congestive heart failure (defined by the occurrence of an acute pulmonary edema requiring an hospitalization), or need for myocardial revascularization. Indications for coronary angiography and myocardial revascularization were based on the clinical course of the patient during follow-up (severe angina class III or IV by the Canadian Cardiology Society under medical therapy, unstable angina, MI). If more than one cardiac event occurred during follow-up, only the most severe event was considered for statistical purposes.

Statistical analysis

The statistical analysis was performed with SPSS software. Results are expressed as means ± SD or n (%). Data comparisons were performed using an unpaired Student t test, a Person χ^2 test, or a Fisher's exact test. Kaplan-Meier survival curves were computed for the occurrence of major and minor events. Comparison of survival curves was performed using a single variable Logrank test. Odd ratios were calculated. Multivariate stepwise Cox regression analyses were computed for the determination of independent predictors of events. The five most relevant variables (according to the univariate analysis) were entered into the model, i.e., age, cardiac medical history, microalbuminuria, ability or inability to exercise, and ²⁰¹Tl SPECT results.

RESULTS**Follow-up**

Complete follow-up was obtained in 100% of the patients. Mean follow-up time was 23 ± 17 months (3–78 months). During follow-up, patients received advice on optimal eradication of associated risk factors. At the end of follow-up, 48 patients with significant ischemia on ²⁰¹Tl SPECT were receiving medical treatment (aspirin $n = 32$, beta-blockers $n = 18$, calcium antagonists $n = 14$, nitrates $n = 15$). Most of these patients were already treated for known or suspected CAD before inclusion.

Table 3 summarizes the occurrence of cardiovascular events. A coronary angiography was performed in 25 patients 15–393 days after inclusion (after MI = 6, after unstable angina = 8, for typical or atypical angina = 8, before major noncardiac surgery

Table 4—Univariate clinical and biological predictors of events

	Event	No event
Cardiovascular death	8	150
Age (years)	74 ± 10	61 ± 9†
BMI (kg/m ²)	22.7 ± 3.0	29.0 ± 5.6†
Personal history of CAD	6 (75)	41 (27)†
Abnormal rest ECG	6 (75)	56 (37)*
Risk factors	5.6 ± 1.5	3.8 ± 1.4†
Microalbuminuria 20–200 µg/min	7 (87)	44 (29)†
Glomerular filtration rate (ml/sec)	0.69 ± 0.29	1.48 ± 0.64†
Fasting glycemia (mmol/l)	12.21 ± 5.99	9.32 ± 3.27*
Nonfatal MI	14	144
Family history of CAD	10 (71)	55 (38)*
Microalbuminuria 20–200 µg/min	8 (57)	43 (30)*
Major event (death or MI)	22	136
Age (years)	67 ± 9	61 ± 8†
Risk factors	4.8 ± 1.8	3.8 ± 1.9†
Family history of CAD	14 (64)	51 (37)*
Personal history of suspected or known CAD	10 (45)	37 (27)*
Peripheral vascular disease	10 (45)	33 (24)§
Fasting glycemia (mmol/l)	10.93 ± 4.55	9.21 ± 3.27*
Microalbuminuria 20–200 µg/min	15 (68)	36 (26)†
Minor event	29	129
Personal history of suspected or known CAD	10 (45)	37 (27)*

Data are n, means ± SD, or n (%). *P < 0.05; †P < 0.01; ‡P < 0.001; §P = 0.07 vs. events.

= 3). Eight, six, six, and five patients had zero-, one-, two-, and three-vessel disease, respectively (defined by a stenosis >50%).

Univariate predictors of cardiovascular events

Clinical and biological parameters. Univariate predictors of death were as follows: age, BMI, history of CAD, abnormal rest ECG, number of risk factors, microalbuminuria, glomerular filtration rate, fasting plasma glucose level, and HbA_{1c} level. Univariate predictors of nonfatal MI were a family history of CAD and microalbuminuria. The only predictor of minor events was a previous history of CAD (Table 4).

EST. There were 78 patients (49%) who were able to exercise and 80 patients (51%) who were unable to exercise. Patients unable to exercise were older (60 ± 9 vs. 54 ± 9 years, P = 0.007), had a higher serum creatinine level (113 ± 85 vs. 85 ± 27 µmol/l, P = 0.007), had a lower glomerular filtration rate (1.25 ± 0.59 vs. 1.62 ± 0.65 ml/s, P = 0.0003), and were more likely to be female (44 vs. 23%, P = 0.007) than patients able to exercise.

Cardiac deaths occurred more frequently in patients who were unable to exercise than in those who were able to exercise (7/80 = 8.75% vs. 1/78 = 1.28%, P

= 0.03) (Fig. 1). There was no difference between patients who were unable and able to exercise regarding the occurrence of MI (8/78 = 10.25% vs. 6/80 = 7.50%, P = 0.37) or minor events (16/78 = 20.51% vs. 13/80 = 16.25%, P = 0.54).

Of the 78 patients who underwent an EST, 48 (61%) had a negative, 20 (26%) a nondiagnostic, and 10 (13%) a positive

EST. In patients with positive EST, duration of exercise was 8 ± 2 min, maximal work load was 110 ± 22 W, maximal heart rate was 90 ± 5% of predicted heart rate, and mean maximum ST depression was 1.9 ± 1.1 mm. Four patients had ST depression ≥2 mm. Major-event and any-event rates were 20 and 50% after a positive EST, 15 and 35% after a nondiagnostic EST, and 8 and 18% after a negative EST, respectively (P = 0.13 and 0.08).

²⁰¹Tl SPECT. ²⁰¹Tl imaging was abnormal in 88 (56%) and normal in 70 (44%) patients. One or more reversible defects were present in 59 patients (37%), and fixed defects were found in 54 patients (34%). Among patients with abnormal SPECT, 31 (35%), 39 (44%), 12 (14%), and 6 (7%) had one, two, three, and four or more abnormal segments, respectively. Univariate SPECT predictors of events are summarized in Table 5.

A major event or a nonfatal MI occurred more frequently after an abnormal than after a normal ²⁰¹Tl SPECT (odds ratio = 5.7, P = 0.03 and odds ratio = 2.9, P = 0.04, respectively). The mean number of abnormal segments was significantly higher in patients with future events. The most accurate threshold value for the prediction of future events was the presence or the absence of more than two abnormal segments (Figs. 2 and 3).

Multivariate analysis: Independent predictors of major events

Independent predictors of major events were as follows: an age >60 years (P =

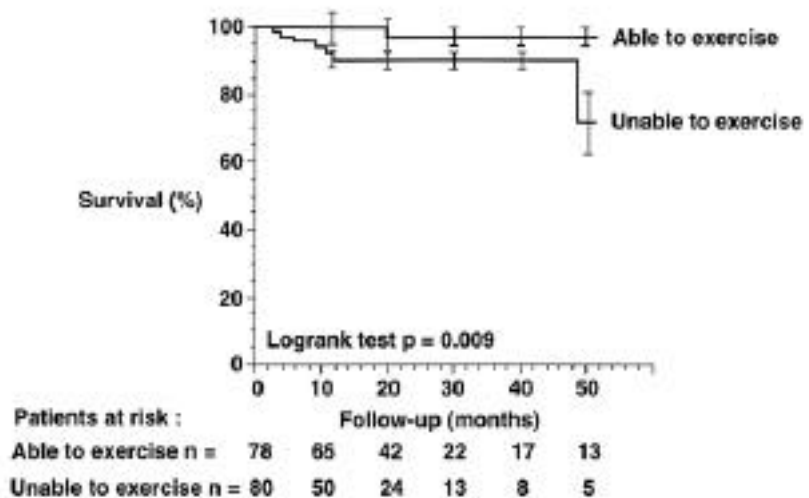


Figure 1—Kaplan-Meier survival curves for the occurrence of cardiovascular deaths according to the ability or inability to exercise. The annual mortality rate was 0.67% in patients able to exercise and 4.59% in patients unable to exercise (odds ratio = 6.83). Error bars represent SEM.

Table 5—Univariate ^{201}Tl SPECT predictors of events

	Cardiac death		Nonfatal MI		Major event		Minor event	
	Event	No event	Event	No event	Event	No event	Event	No event
<i>n</i>	8	150	14	144	22	136	29	129
Abnormal SPECT	6 (75)	82 (54)	12 (86)	76 (53)*	18 (81)	70 (51)*	17 (59)	71 (55)
Number of abnormal segments	2.1 ± 2.6	1.0 ± 1.2†	1.7 ± 1.4	1.0 ± 1.3*	1.8 ± 1.8	0.9 ± 1.2†	1.4 ± 1.8	1.0 ± 1.2‡
Number of reversible segments	1.0 ± 1.0	0.6 ± 0.7	1.1 ± 1.0	0.5 ± 0.7*	1.0 ± 1.0	0.5 ± 0.8†	0.8 ± 1.0	0.5 ± 0.8
Number of fixed segments	1.1 ± 1.3	0.4 ± 0.7†	0.6 ± 0.4	0.5 ± 0.7	0.8 ± 0.9	0.4 ± 0.7*	0.6 ± 0.8	0.5 ± 0.7
>2 abnormal segments	4 (50)	14 (9)†	4 (28)	14 (10)§	8 (36)	10 (7)	7 (24)	11 (9)*
≥1 anterior wall defects	2 (25)	26 (17)	4 (29)	24 (17)	6 (27)	22 (16)	6 (21)	22 (17)
Lung-to-heart ratio	0.37 ± 0.01	0.33 ± 0.01*	0.39 ± 0.01	0.37 ± 0.01§	0.37 ± 0.01	0.37 ± 0.01	0.47 ± 0.02	0.35 ± 0.01†

Data are *n* (%) or means ± SD. An abnormal SPECT indicates the presence of at least one hypoperfused segment. * $P < 0.05$; † $P < 0.01$; ‡ $P = 0.08$; § $P = 0.06$; || $P < 0.001$ vs. events.

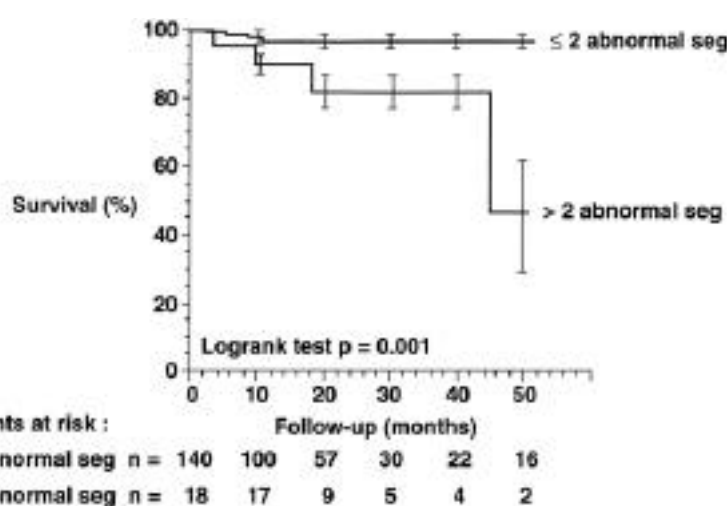


Figure 2—Kaplan-Meier survival curves for the occurrence of cardiovascular deaths according to the presence or absence of more than two abnormal segments on ^{201}Tl SPECT. The annual mortality rate was 1.46% in patients with less than or equal to two abnormal segments and 11.59% in patients with more than two abnormal segments (odds ratio = 7.78). Error bars represent SEM. seg, segments.

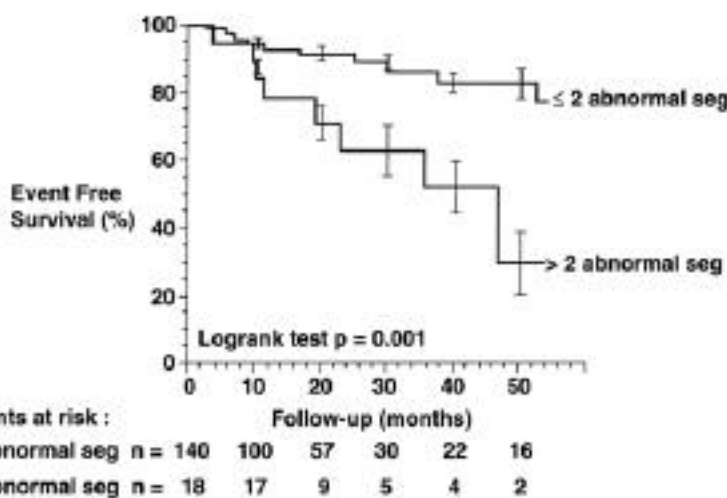


Figure 3—Kaplan-Meier survival curves for the occurrence of major cardiovascular events (death or myocardial infarction) according to the presence or absence of more than two abnormal segments on ^{201}Tl SPECT. The event rate was 5.20% in patients with two or fewer abnormal segments and 23.26% in patients with more than two abnormal segments (odds ratio = 4.44). Error bars represent SEM. seg, segments.

0.02), a personal history of CAD ($P = 0.04$), the presence of a microalbuminuria ($P = 0.001$), the inability to perform an EST ($P = 0.002$), and the presence of an abnormal ^{201}Tl SPECT ($P = 0.03$) or of more than two abnormal segments on ^{201}Tl SPECT ($P = 0.002$). (Fig. 4).

The positive (PPV) and negative (NPV) predictive values of the presence or absence of more than two abnormal SPECT segments were 0.22 and 0.97 for cardiac deaths, 0.44 and 0.90 for major events, and 0.39 and 0.85 for minor events, respectively. Similarly, the PPV and NPV of a normal and abnormal ^{201}Tl SPECT were 0.07 and 0.97 for cardiac deaths, 0.20 and 0.94 for major events, and 0.24 and 0.83 for minor events, respectively. In patients unable to exercise, ^{201}Tl SPECT accurately stratified patients with higher and lower risk for future cardiovascular death. Indeed, a death occurred in 3 of 7 patients (42.8%) with more than two abnormal segments, but in only 4 of 73 patients (5.4%) with two or fewer abnormal segments (odds ratio = 7.9, $P < 0.005$) (Fig. 5).

CONCLUSIONS

Rationale of the study

The prevalence of CAD in NIDDM patients is 43–53% (1,2,30), regardless of sex (3). Ischemia is more often silent in these patients (6,7), and 50–70% of them die from cardiovascular cause (1,31). Detection of high-risk diabetic patients is of great interest because they may benefit from specific approaches such as vigorous eradication of risk factors (32), medical therapy (33,34), or myocardial revascularization (35). Since 5–8% of the population suffers from NIDDM, cost is a major issue. A cost-effective screening must lead to invasive strategy only in patients who will benefit from revascularization, and the use of non-

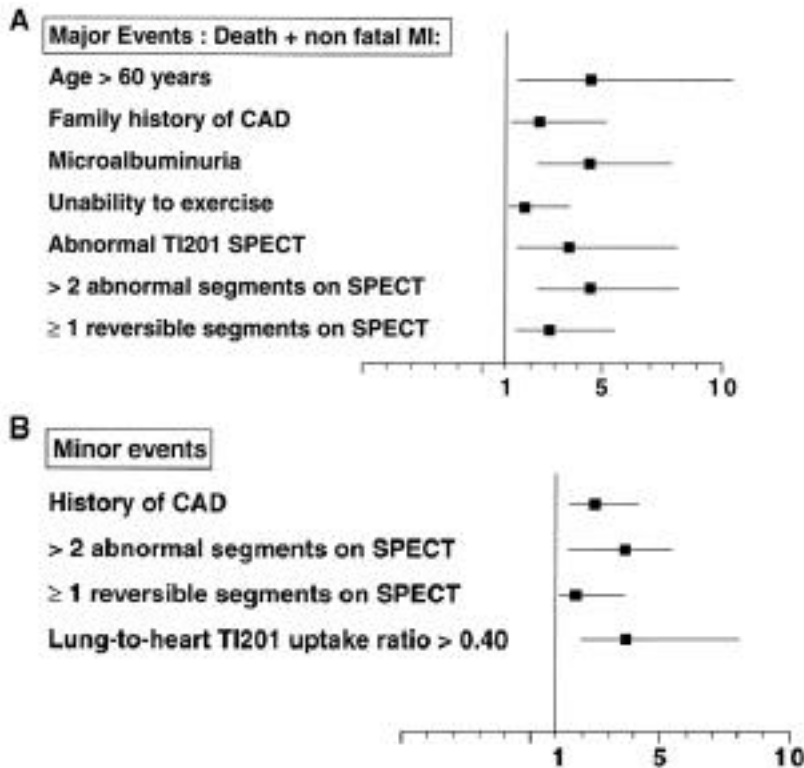


Figure 4—Odds ratios and 95% CIs for the occurrence of major (A) and minor (B) events, according to multivariate Kaplan-Meier analysis.

invasive tests should be limited to a subset of high-risk patients. Although all diabetic patients may benefit from aggressive correction of associated risk factors, a noninvasive screening of all diabetic patients does not seem justified, since NIDDM patients with less than two cardiovascular risk factors have an age-adjusted annual cardiovascular mortality rate of only 0.3–0.6% (2). Conversely, in NIDDM patients with two or three risk factors, the annual cardiovascular mortality rate rises to 1.2–5.4% (2,36).

Accordingly, only NIDDM patients with more than two risk factors were included in the present study. We considered classic risk factors (smoking, hypertension, dyslipidemia) (2), as well as other criteria already identified, to be of predictive value in NIDDM (age >65 years, history of CAD or peripheral artery disease, abnormal rest ECG, microalbuminuria) (2,4,11,37). We focused on the prognostic values of EST and ²⁰¹Tl SPECT in such patients, since the design of the study was to perform an EST coupled with ²⁰¹Tl SPECT in patients able to exercise, while patients unable to exercise were proposed for a dipyridamole scan. Our study confirms that some factors are predictive of future major events: age, history of CAD, rest ECG, BMI, microalbuminuria, and decreased glomerular filtration rate. Peripheral vascular disease was also more frequent in patients with future major cardiac events, although this relationship did not reach a significant statistical level ($P = 0.07$). These findings are consistent with the established association between peripheral artery disease and CAD in the general and NIDDM populations. The study popu-

lation was not, however, large enough to assess the relationship between the occurrence of cardiac events and a previous history of stroke.

Patients able to exercise were of relatively good prognosis in comparison with patients unable to exercise, with death occurring seven times more frequently in patients unable to exercise, consistent with previous studies suggesting that decreased exercise performance may signal coronary heart disease in NIDDM patients (13). Poor exercise capacity has also been shown to be associated with the presence of microvascular complications in NIDDM patients (38), and the poor prognostic value of low functional capacity has been confirmed in a large nonselected population of patients referred for ²⁰¹Tl scintigraphy (39). To our knowledge, however, no data are yet available specifically assessing the prognostic value of EST in NIDDM patients. Our study does not demonstrate that EST is of additive prognostic value per se in high-risk NIDDM patients. However, there is a trend toward a higher major event rate after a positive EST than after a normal EST.

Concerning Tl201 SPECT, the prevalence of abnormal scans in our population was 47%, consistent with the values of 17–48% previously reported in nonselected diabetic patients (19,20). The main finding of our study is that ²⁰¹Tl imaging is an independent predictor of future cardiovascular events. Especially, the presence of a large defect, involving more than two myocardial segments, accurately identifies higher-risk patients, as already suggested (20). Indeed, such a large defect more

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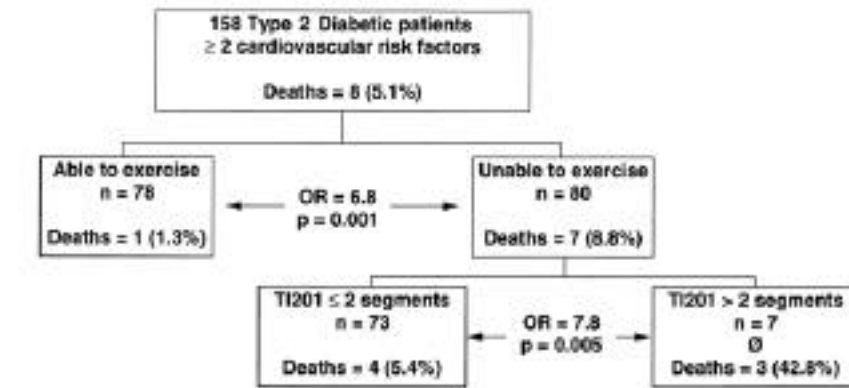


Figure 5—Flow chart representing the incremental prognostic value of dipyridamole ²⁰¹Tl myocardial perfusion imaging in patients unable to exercise. Cardiovascular deaths occur in 8.8% of patients unable to exercise. Among these patients, death occurs in 5.4% of patients with ≤ 2 abnormal segments or ²⁰¹Tl SPECT vs. 42.8% of patients with > 2 abnormal segments. OR, odds ratio.

likely reflects the presence of multivessel disease or a large amount of jeopardized myocardium. This subset of very high-risk patients, representing 11.4% of our population, has an annual mortality rate of 10%, i.e., a three times increase of age-adjusted pretest likelihood of death and a seven times increased probability of death when compared with patients with normal SPECT. We also found that the number of reversible defects was related to the occurrence of future MI, while the number of fixed defects was related to the occurrence of future cardiac death. These findings are consistent with the data available in nondiabetic patients. Indeed, fixed defects reflect irreversibly injured myocardium and altered left ventricular function and are therefore predictive of future death, while reversible defects are correlated with the amount of jeopardized myocardium and are more predictive of future ischemic events (40).

An important finding is that the NPVs of ^{201}Tl SPECT for the occurrence of major cardiac events and death are 94 and 97%, respectively. This value, which is slightly lower than that reported in patients with low-to-intermediate probability of CAD (14,15) or before vascular surgery (41), may be explained by a higher pretest likelihood of future events in our selected population, or by a lower sensitivity and specificity of ^{201}Tl SPECT in these patients (microvascular disease, left ventricle hypertrophy, endothelial dysfunction). Furthermore, cardiovascular risk in NIDDM is not only related to the presence of epicardial CAD, but also to diverse mechanisms that affect myocardial function and myocardial blood supply (42–44). The prognostic value of ^{201}Tl SPECT myocardial perfusion imaging remains debated in diabetic patients (19–26,45). Interestingly, studies including higher risk diabetic patients, based on clinical stratification (22,23), reported a higher prognostic value of myocardial perfusion imaging than studies including nonselected patients (19,20,24–26).

Another major finding is that ^{201}Tl SPECT has an incremental prognostic value over clinical and biological variables, the presence of an abnormal scan, and especially of more than two abnormal segments, being independent predictors of outcome. Furthermore, ^{201}Tl SPECT has significant additive prognostic value in patients unable to exercise, the risk of death being 7.8 times higher when a large perfusion defect is present.

Limitations of the study

Because of the low event rate in patients able to exercise, it was not possible to demonstrate whether ^{201}Tl SPECT adds significant prognostic information over EST, as shown in other populations (14). However, there was a trend toward a higher event rate in patients with positive EST than in those with negative EST. It is, therefore, reasonable to hypothesize that a perfusion scan may be of additive value in these patients.

Our study demonstrates the poor prognosis of patients with large perfusion defects, particularly in those unable to exercise. It does not demonstrate that revascularization will improve the prognosis of such patients, and only a large randomized trial could answer this point. However, in the subset of patients undergoing coronary angiography and presenting large perfusion defects, multiple vessel-disease and/or impaired left ventricular function was observed in most cases. In these circumstances, bypass revascularization, as well as medical therapy and vigorous eradication of risk factors, are known to improve prognosis (31–34).

Because of the selection bias in our study (NIDDM patients with two or more risk factors), prevalence of CAD, and therefore of future cardiac events, is higher than that of the general NIDDM population. It is, therefore, possible that our findings may not be applicable to other NIDDM patients. Such risk assessment is, however, probably less useful in patients with lower pretest likelihood of CAD and requires further evaluation.

Clinical implications

In clinically selected high-risk diabetic patients, ability to exercise is related to a low probability of future cardiovascular events, and ^{201}Tl SPECT has little additive value in this case. Conversely, inability to exercise is associated with a high risk of events, and ^{201}Tl imaging adds incremental prognostic value, the presence of more than two abnormal segments identifying a very high-risk subset of patients. As already proposed for the diagnosis of CAD (46), we suggest that for purposes of prognosis, a dipyridamole ^{201}Tl SPECT should be performed in asymptomatic high-risk NIDDM patients unable to exercise or to achieve a maximal EST.

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